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THE SIGNIFICANCE OF ZINC IN THE LIVING ORGANISM*

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IN THE course of a general investigation upon the hygiene of zinc, now being carried out in the Department of Physiology of the Harvard School of Public Health, it has been necessary, in addition to our experimental work, to make a somewhat extensive review of the literature on zinc in all of its biologic aspects. In a review of this sort, one is struck, on the one hand, by the very widespread normal occurrence of zinc, by reports of its existence in soils, in plants, in marine organisms, in practically all foodstuffs, in all animal organs and tissues, and in the excreta of normal animals, and yet, on the other hand, by the fairly general failure of investigators to recognize this normal universality of zinc, or to take it into consideration in their reports of the finding of zinc in organs and excreta.

In an attempt to evaluate the toxicity of zinc industrially or to determine in a given case of illness whether or not zinc is a toxic agent, it is obviously important to possess accurate information upon the amounts of zinc normally present in the mammalian body and normally excreted by it, and to understand as clearly as possible the significance of zinc in normal metabolism. It is clearly absurd to diagnose zinc poisoning from the finding of 1 or 2 mg. of zinc in the urine, when one knows that normally an adult excretes daily by this route 0.25 to 1.5 mg. of the metal in question. It is equally unjustifiable to infer, as Seiffert (1) has done,

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that there are large abnormal deposits of zinc in the bodies of workmen because zinc is found in their urines long after they have ceased employment in a zinc industry. The normal zinc excretion, though fairly constant within a given range on an ordinary mixed diet, will increase markedly if foods rich in zinc, such as oysters, are eaten. Facts such as these have seldom, if ever, been taken into consideration in diagnoses of industrial zinc poisoning or in discussions of the absorption and excretion of zinc following the inhalation of smelter fumes. Understanding of the normal occurrence and rôle of zinc in the mammalian body is, therefore, fundamental to an intelligent attempt to evaluate the effects of abnormal amounts of zinc introduced into it in the course of exposure to industrial processes.

Not only is zinc universally present in animal tissues and in by no means negligible quantities, but it has also been shown recently to be present in remarkably similar total concentrations in animals of different species and in approximately constant concentrations in different animals of the same species. Besides analytically demonstrated facts such as these, suggesting a probable importance of zinc in the normal body metabolism, there is a good deal of evidence to be found here and there in the literature of a biologic activity on the part of zinc. So suggestive, indeed, has this evidence appeared to us, that we have thought it worth while to present in a brief paper the opinions of a number of investigators on this matter, together with a summary of the experimental data which leads us to believe that zinc is indispensable for the normal functioning of the body.

Universality and Uniformity of Zinc Occurrence

Plants

In a paper recently published from this laboratory, Lutz (2) has summarized the observations already reported upon the existence of zinc in the various forms of plant life. Zinc is present in by no means negligible quantities in trees, in all phanerogamous plants, in molds, algae, grains of all sorts (corn, wheat, barley, oats, rye), tubers, vegetables, greens (spinach, cabbage, lettuce), and fruits (oranges, apples). In considering the question of zinc in plants, McHargue (3) has noted that zinc occurs in the leaves, and in the pericarps and germs of seeds, and has commented on the desirability of adding small amounts of copper, manganese, and zinc to soils depleted of these metals in order to restore and maintain productivity and to produce a food supply containing the vital factors in normal proportion.

Animals

But plants and their products represent only a small fraction of the biologic storehouses of zinc. This metal is present in all sorts of marine organisms (conch, crayfish, sea cat, tunicate, oyster, clam, herring, sea lion, whale, etc.), in reptiles, in fowl, in eggs, in milk, and in the blood, the gastro-intestinal tract, the liver, the kidneys, the pancreas, the spleen, the lungs, the thymus, the mammary gland, the reproductive glands, the brain and spinal cord, the muscle, the bone, the skin, the hair, the hoof—in

fact, in every tissue and every organ of the various species of animals studied. Lutz has reviewed extensively the data upon zinc in animal tissue and has added many figures of his own on the normal zinc content of the rat, cat, and man.

That zinc cannot be accidentally present but that it must have some definite rôle to play in bodily processes is suggested, not only by its universality, but also by the remarkable uniformity of its concentration in the same tissues of different members of the same species, and by the striking fact that the average total concentration of zinc is approximately the same in animals of one species, regardless of age and weight.[1] Lutz' own figures illustrate these points admirably. In analyses of the livers of nine rats, for example, the amount of zinc in milligrams per gram ranged from 0.0182 to 0.0238; in kidneys, from 0.011 to 0.019 (seven animals); in blood, from 0.0054 to 0.0075 (nine animals). Figures from cats showed the same uniformity. Blood from four cats showed a range of zinc concentration in milligrams per gram of 0.0042 to 0.0051; kidneys, from 0.0122 to 0.0157 (four animals); pancreas, from 0.0231 to 0.0277 (three animals); hair, from 0.2087 to 0.2414 (three animals); brain and spinal cord, 0.009 to 0.01 (three animals). These are illustrations only. With few exceptions, a rat organ or a cat organ will show very nearly the same zinc concentration as the same organ in another rat or another cat. This fact is the more noteworthy when we consider that the initial weights of the rat tissues studied by Lutz showed a wide range, indicating that animals of different ages were represented.

This constancy of zinc concentration regardless of age is further shown by the total zinc concentrations found by Lutz in a series of rats ranging in weight from 41 gm. (approximately three weeks old) to 261 gm. (approximately twenty-three weeks old). We have recently amplified Lutz' series by analyses on eight newborn rats of 4.1 to 5.31 gm. in weight. Table 1 presents Lutz' data. Table 2 gives figures obtained in this laboratory by Dr. Phebe K. Thompson on eight rats taken for analysis within twenty-four hours of birth. The similarity of the zinc concentration in all of these animals is very striking.

Analyses on cats, by Lutz, confirmed his rat findings so far as uniformity of total zinc concentration was concerned (see Table 3). The cats were, however, all adult animals.

Comparing the figures for total zinc concentrations obtained by various observers in different mammals, Lutz commented as follows:

> The total zinc concentration in rabbits one to four months old [according to Bertrand and Vladesco (4)] was from 44 to 49 mg. per kilogram, in mice from 25 to 42 mg., and in

[1] Bertrand and Vladesco (4) would take exception to this statement, their opinion being that the zinc concentration is highest at birth or shortly after, that it then diminishes gradually to a minimum, and then shortly increases up to the time of old age. In our opinion, their figures do not warrant such a conclusion. With the exception of two very high figures—for a year-old fowl and for five young fish—the zinc concentrations reported by Bertrand and Vladesco for mice, rabbits, guinea-pigs, fowl, and three kinds of fish seem to us to show, in the main, a fairly close uniformity for each species, especially when one takes into consideration the fact that the method of analysis employed was not at all comparable in accuracy or in delicacy to that used by Lutz and by Thompson.

the guinea-pig from 23 to 56 mg. (two observations). These results suggest the interesting possibility that the total zinc concentration varies but little in animals of different species. My findings of 29.4 mg. of zinc per kilogram for the rat and of 33.2 mg. per kilogram for the cat offer confirmatory evidence on this point.

TABLE 1.—NORMAL ZINC CONTENT OF RATS RANGING IN AGE FROM THREE TO TWENTY-THREE WEEKS[1]

RAT NO.	WEIGHT OF RAT	TOTAL ZINC FOUND	CONCENTRATION OF ZINC
	gm.	*mg.*	*mg. per gm.*
1	41.0	1.23	0.0300
2	55.0	1.77	0.0322
3	98.0	2.59	0.0264
4	113.0	2.51	0.0222
5	206.0	7.10	0.0345
6	211.0	5.74	0.0272
7	224.0	7.46	0.0333
8	233.0	7.53	0.0323
9	261.0	6.72	0.0257
10	261.0	7.86	0.0301
Average			0.0294

[1] Data from Lutz (2).

TABLE 2.—NORMAL ZINC CONTENT OF NEWLY BORN RATS

RAT NO.	WEIGHT OF RAT	TOTAL ZINC FOUND	CONCENTRATION OF ZINC
	gm.	*mg.*	*mg. per gm.*
1	4.10	0.16	0.0390
2	4.71	0.15	0.0318
3	4.71	0.15	0.0318
4	4.53	0.14	0.0309
5	4.25	0.10	0.0235
6	4.90	0.20	0.0408
7	5.31	0.21	0.0395
8	5.00	0.14	0.0280
Average			0.0332

The bloods of different species as well as the total zinc concentrations show a remarkable similarity (2).

TABLE 3.—NORMAL ZINC CONTENT OF ADULT CATS[1]

CAT NO.	WEIGHT OF CAT	TOTAL ZINC FOUND	CONCENTRATION OF ZINC
	kg.	*mg.*	*mg. per gm.*
1	3.06	111.49	0.0364
2	3.36	107.19	0.0319
3	3.32	103.45	0.0312
Average			0.0332

[1] Data from Lutz (2).

Rats' blood, for example, contains an average zinc concentration of 0.0067 mg. per gram; cats' blood, 0.0046; dogs' blood, 0.004 to 0.005; human blood, 0.0052. This similarity is the more striking in that these four species exist on such totally different diets.

Lutz' figures on the zinc concentration of tissues are much more uniform than those of other observers—a fact probably due to his use of a new method of zinc analysis, more accurate and more delicate than any hitherto applied to biologic material. With the exception of man, the groups of animals studied by Lutz were on an approximately constant diet—that is, a diet constant in quality for each species. There was no especial limit to the amount available.

The total amount of zinc present in the animal body, as well as its universality, is worthy of comment. Calculating on the basis of the zinc concentrations obtained by Lutz in the total rat and the total cat, which are very close when reduced to an

equivalent weight basis, the total zinc content of a man weighing 70 kg. is approximately 2.2 gm., a figure not far from the 2.8 gm. of iron estimated to be present in a man of this weight.

Evidence of Biologic Activity

Interesting and suggestive as these chemically demonstrated facts are in regard to the universal and uniform occurrence of zinc, we require, in addition, evidence of biologic activity and indispensability before we may legitimately regard zinc as an essential factor in plant and animal metabolism. Let us then consider the evidence available upon these matters.

Plants

As long ago as 1869, Raulin (5), a pupil of Pasteur, seeking the best nutrient solution for the culture of the mold fungus, Aspergillus niger, came to the conclusion that zinc was indispensable for the development of this mold. The usefulness of the metal was determined by drying and weighing the fungus after a few days of growth in a nutrient solution containing zinc and comparing the weight thus obtained with that of a control culture. Raulin had 2 to 4.6 times as favorable results with zinc as he had without it. Richards (6), in 1897, working with the same fungus, believed that zinc was not indispensable but was a stimulant.

Between the years 1907 and 1914, Javillier, working part of the time with Bertrand, studied intensively the effect of zinc on Aspergillus niger (7).[2] Javillier, first working alone, determined that small amounts of zinc added to the nutrient fluid in which this fungus was grown promoted its growth markedly. He also showed that Aspergillus made use of zinc when it was present in its culture medium even in extreme dilutions; he determined the optimum concentrations of zinc for the culture of the mold; and showed that growth fell off and then ceased as the zinc concentration was increased above the optimum percentage. In 1911, Bertrand and Javillier ascertained that zinc and manganese singly, and most noticeably when used together, increased not only the growth but also the total mineralization of the plant. These experiments "besides their practical interest, tend to show that zinc and manganese are not merely active excitants of protoplasm. In close quantitative relation to the total substance of the plant, zinc and manganese are not only active elements, but they are also indispensable intermediaries in chemical transformations of which the living cell is the seat."

Writing in 1912 under the title, "Influence of Zinc on the Consumption by *Aspergillus Niger* of Carbohydrate, Nitrogenous and Mineral Foods," Javillier reported the following observations. In a medium containing zinc, the consumption of sugar by Aspergillus was constant; without zinc, the relation was not constant. The plant consumed more sugar without zinc than when zinc was present. The "expense of upkeep" was greater without zinc. Without zinc, Asper-

[2] A certain amount of controversy exists in the literature in regard to Javillier's work but, undoubtedly, the great bulk of experimental evidence—and it comes from a number of different investigators—supports his observations.

gillus also used a greater proportion of ammoniacal nitrogen for the construction of 1 gm. of plant than with zinc. The presence of zinc, however, caused a greater use of mineral elements by the plant. More silicon and phosphorus were used, and less sulphur; very slightly more potassium. Of the elements which Javillier called catalytic, iron and manganese accumulated in greater proportion in the presence of zinc, and magnesium in less quantity. In further studies on the physiologic effect of zinc on mold, yeast, and certain phanerogamous plants, Javillier found that Aspergillus, deprived of zinc, did not diffuse sucrase into the culture medium. The cells, however, secreted sucrase sufficient to invert rapidly the saccharose which was offered them, but the quantity secreted in relation to the weight of the plant was noticeably less than in the presence of zinc, and the diastase disappeared rapidly from the mycelium. Javillier also showed that the presence of zinc in the culture liquid caused considerable increase in the growth of yeast, quite analogous to, though not quite so great as, the effect on Aspergillus niger.

Although he experimented with a great variety of other metals, Javillier was able to find only one, cadmium, which had an effect on Aspergillus at all comparable to zinc, and this effect was much less marked. His experiments led him to conclude that the action of zinc is a specific one and that this element has a distinct physiologic character.

Bertrand (8), in 1912, stated that elements present in the soil in very small amounts were just as necessary to the general metabolism as carbon and nitrogen. They seemed to act as catalyzers. Experimenting at this time with zinc as a catalytic fertilizer, Javillier (7), using 1 to 10 kg. of zinc sulphate to the hectare (about $2\frac{1}{2}$ acres), found the increase in dry weight of maize to be 18 to 25 per cent. in the best cases, and 5 per cent. in the worst. With other plants, beneficial results were not constant enough to permit conclusions.

Hans Reese (9), also in 1912, confirmed the favorable effect of zinc on the growth of Aspergillus niger. The effect of the zinc, in this author's opinion, consisted principally in a very strong acceleration of the development of the mycelia, so that the difference in harvest between zinc free and zinc containing cultures was much greater after four than after six days. Reese found manganese favorable, but in general less effective than zinc, and confirmed the results of Bertrand and Javillier on the beneficial effect of using zinc and manganese together. The accelerating influence of zinc was so much greater than the final furthering influence that Reese thought this fact might be a cause of contradictions in the literature. Acceleration concerned only vegetative development, not spore formation.

Kostychev and Zubkova (10) reported in 1916 that the formation of acetaldehyde by dry yeast under the action of zinc salts depended upon the influence of the zinc ion. Cadmium salts exerted a similar but more energetic action during fermentation of sugars but not during autolysis in the presence of water. The action of zinc and of cadmium was specific. Analogous effects were not obtained with salts of calcium, magnesium,

strontium, mercury, antimony, and aluminium.

In 1919, "A Study of Some Factors in the Chemical Stimulation of the Growth of *Aspergillus Niger*" was published by Steinberg (11), an American. He confirmed the results of Raulin, Richards, Javillier, and Reese concerning the favorable effect of zinc on the growth of Aspergillus niger, and showed that increase in the acidity of the nutrient solution supplemented the action of the heavy metals, while decrease in acidity detracted from their action. The salts of the heavy metals which act as stimulants hydrolyze in aqueous solution so as to result in increased acidity, an increase which probably supplements the action of the metal itself. Steinberg's experiments showed a parallelism between increase in growth, retardation of fructification, and increase in acidity.

A study of "The Problem of the 'Economic Coefficient' in *Aspergillus Niger*" (also discussed by Javillier (7) and Pfeffer (12)) was published in 1922 by Butkewitsch and Orlow (13). These investigators found that zinc sulphate produced a marked acceleration of mycelial development and an increase in the economic coefficient. Experimenting also with salts of mercury and of cobalt, they found a slighter stimulation than when zinc was used, but better results than were obtained with a culture liquid without any stimulating salt. By economic coefficient these authors meant the relation between growth of the fungus and the amount of material needed in growth.

Some interesting experiments by Mazé (14) have brought to light further evidence of the biologic importance of zinc to plants. This observer showed that the suppression of zinc in the nutritive liquid in which maize was grown rendered the maize rapidly and markedly chlorotic, not by a chlorosis from the lack of iron or from the absence of sulphur, but by a toxic chlorosis of alimentary origin. Other experiments also suggest that zinc may hinder in the tissues the production or accumulation of injurious products derived by metamorphosis from food substances (Piccinini (15)).

Animals

Bradley, and later Bradley and Mendel (16), studying the occurrence and function of copper and zinc in Sycotypus, have shown these metals to be present in the blood and the liver of this mollusc. According to these authors, "the real significance of the zinc and copper in the liver of Sycotypus is probably to be looked for in the constant occurrence of these elements in the blood. Zinc is perhaps an essential element of the respiratory proteid of this mollusc and the allied Fulgur carica. . . . . The presence of the zinc in the liver is thus of secondary importance; for that organ acts regularly as the storehouse for reserve elements required in the processes of haemopoiesis and respiration."

Severy (17), also studying the occurrence of copper and zinc in marine organisms, has noted the fact, already well known, that copper is present in the lower forms of sea animals as an oxygen carrier in place of the iron of mammals. The function of zinc, however, which was found in all of the great variety of forms studied, is, according to Severy, not clearly under-

stood, but it may be present as an aid to enzymic action. Bradley and Mendel (16) reported that of the total ash of the liver of Sycotypus copper comprised about 8 per cent., zinc about 15 per cent. The copper was uniformly distributed in small quantities in the gland cells and in the connective tissue, but was present in especially high percentages in the greenish pigment cells. Zinc was found especially in the gland cells of the liver, being twice as abundant there as in the connective tissue. We comment particularly on this special localization of zinc in the actively functioning glandular cells as contrasted with the supporting connective tissue cells, because we have evidence tending to show a connection between zinc and the growth and functional activity of cells and cellular secretions. This evidence consists of a number of different facts, apparently unrelated, which have been interpreted differently by different observers, but which, in our opinion, may be clues to the biologic function of zinc and are, at any rate, suggestive stimuli for further investigation.

Cristol (18), for example, in studies on the occurrence and significance of zinc in tumors, showed that in benign connective tissue tumors zinc was slightly increased above the normal; in epithelial tumors, on the contrary, the increase was much more marked—0.259 to 0.367 parts per 1,000 parts of dry matter in the former as against 0.316 to 1.49 parts of zinc per 1,000 in the latter. The zinc content depended on the nature of the tumor; the greater the amount of connective tissue, the less the zinc; the amount of zinc was parallel to the degree of karyokinesis; the more rapid the evolution of the tumor, the greater was the zinc content. These results tend to show that the zinc content of cancerous tissue is a function of the cellular and nuclear activity. Cristol also reported in a case of leukemia that the zinc content of the blood, of the liver, and of the spleen was much increased over the normal. The figures recorded, in terms of grams of zinc per kilogram of dry material, were as follows: normal liver, 0.356; leukemic liver, 1.231; normal spleen, 0.198; leukemic spleen, 0.996; normal blood, 0.139; leukemic blood, 2.651. Both of the pathologic conditions studied by Cristol—carcinoma and leukemia—are striking instances of exaggerated cell metabolism. The increase, therefore, in the zinc concentration in the abnormal cells over normal cells of the same type suggests a correlation between zinc and growth processes—a correlation for which Javillier's work, and that of others, on Aspergillus niger has already prepared us.

Piccinini (15), in an interesting article on "Zinc in the Animal Organism and its Physiologic Function," suggested that the physiologic office of zinc might be summarized as that of a biologic catalyzer. In support of this idea, he adduced the work of Delezenne (19), who attempted to correlate enzymic activity and zinc content on the theory that the zinc might be the chemically active element of the enzyme. In this connection, Delezenne showed that zinc was present in snake venoms in a very stable combination, that the amounts of zinc paralleled the intensity of the venom actions, and that the relative

activity of the nuclease of the various venoms studied closely corresponded to the zinc content. Delezenne believed that zinc was a specific component of this particular enzyme.

Further indication of the possible importance of zinc in normal growth processes seems to us to exist in figures reported by Birckner (20) on the zinc content of egg yolk and of milk. In hens' eggs practically all the zinc is contained in the yolk—the material upon which the embryo depends for its growth. White of egg contains a mere trace of the metal. The total amount of zinc present is about 1 mg. per egg. The zinc content of ordinary market milk averages about 4.2 mg. of metallic zinc per kilogram of milk. The figure varies somewhat in different animals and is highest during the early parts of lactation, falling off markedly when an animal becomes nearly dry. This is significant since the early weeks of lactation are the time of greatest growth on the part of the offspring. The zinc content of human milk, oddly enough, is markedly higher than that of cows' milk and increases rapidly in concentration during the early days of the puerperium. Birckner, for example, found the following amounts of zinc in the milk of a negro mother: fourth day after parturition, 5.66 mg. per kilogram of fresh substance; ninth day, 11.5 mg.; fifteenth day, 13.78 mg. This author concluded his paper with the following sentence: "From its constant occurrence in the yolk of eggs as well as in cow's and human milk, it is inferred that the element zinc exerts an important nutritive function, the nature of which is not at present understood."

A number of papers dealing with the occurrence and the rôle of zinc in the vertebrate organism have been published by Bertrand and his various associates—Vladesco, Benzon, and Nakamura (4) (21). Of special interest to us is an article entitled "The Probable Intervention of Zinc in the Phenomena of Fecundation in Vertebrate Animals." Observations on herring during a period of sexual activity, the month of March, showed that the testicles and milt contained more than twice as much zinc per 100 gm. of dry matter as the muscles and skeleton. At the end of the active season in May, the testicles contained less than one-half as much zinc per 100 gm. of dry matter as the muscles and skeleton. Figures are given on the amounts of zinc in various portions of the male reproductive tract of different species, and the high zinc content of the prostate and of seminal fluid is stressed. The paper reads:

> In man, the prostate is richer than the testicles; its content of zinc surpasses that of all the other organs of the body analyzed up to now. . . . .
>
> Finally, in the course of our experiments, we have determined that semen, a mixture of the secretion of all the glands of the reproductive apparatus, contains a very remarkable proportion of zinc, even reaching 2 gm. per kilogram of dry material. . . . .
>
> After these observations and those which we have already published, it seems to us permissible to suppose that zinc plays an important and very general rôle in the vertebrate organism: it probably plays some part in the function of reproduction and, if one takes into account its mobility, without doubt it plays a part also in the processes of regulation and of internal secretion.

Bertrand and his associates have provided us with the only experimen-

tal evidence which exists upon the effect on mammals of zinc deprivation. Bertrand and Benzon compared two lots of mice of the same litter, fed, one lot with zinc free food, the other lot with the same ration plus a small known quantity of zinc. The process of rendering the ration zinc free involved inevitably the destruction of nearly all vitamins, so that in the end all the mice died as a result of vitamin deprivation.

The mice which received zinc, however, in an amount comparable to that in a normal diet, survived 25 to 50 per cent. longer than their brothers and sisters subsisting upon the zinc free diet. The authors summed up their findings as follows:

> Zinc has behaved, in experiments on the synthetic feeding of mice, as an element of great physiologic importance. In animals subjected to a diet completely free of zinc, the organism has retained with great tenacity the small supply of the metal which it possessed at the beginning of the experiments; in animals which were fed with the same food plus the addition of a small amount of zinc, comparable to that which they would have received on a natural diet, there was an accumulation of the metal sufficiently great for the original content of it to be almost doubled. Finally, in each series of experiments, the animals that were given zinc in their food lived longer than those which did not have it. The importance of the metal was such that a tenth and a half to three-tenths of a milligram, ingested during the entire length of one experiment, was sufficient to prolong its duration 25 to 50 per cent. It is not yet possible to affirm, but it seems highly probable, that if the other factors of growth had not been lacking, these results would have been still further exceeded.

Further experiments by Bertrand and Nakamura in which mice were fed on the diet used in Bertrand's first set of experiments, with the exception that it contained no iron, showed that mice lived longer when deprived of iron than they did when deprived of zinc. The authors concluded their paper with the following statement:

> If we compare now the results of our experiments on zinc with those on iron, one ascertains clearly that the effects of deficiency are more extensive in the first case than in the second. The researches which we report today not only provide a direct demonstration of the rôle played by iron in nutrition, but they furnish also a new proof of the physiologic importance of zinc.

Summary

The universal occurrence of zinc in all types of plant and animal life; the striking uniformity of zinc concentration in animals of different species (mammals), in animals of the same species regardless of age and weight, and in the same tissues of different members of the same species; the very considerable total amounts of zinc present in animals—these facts all suggest that zinc very probably plays some significant part in the normal metabolism of plants and of animals. The probability of a biologic activity on the part of zinc, suggested by these chemically demonstrated facts, is further strengthened by evidence derived from a variety of plant and animal experiments. The importance of zinc in the development of Aspergillus niger; the chlorosis which develops when corn is deprived of zinc; the parallelism between the zinc content and the rate of growth of certain cells, and between the zinc content and the activity of certain cellular secretions; the high zinc content of sub-

stances, such as yolk of egg and milk, which represent the normal sources of nutriment for developing organisms during periods of extremely active growth; the high zinc content of spermatic fluid; and, finally, the more rapid death of animals on a zinc free diet than that of animals on a similar diet to which a small amount of zinc has been added—these facts constitute convincing experimental evidence of a biologic importance of zinc. The exact rôle that zinc plays in plant and in animal metabolism is by no means understood. The indications are, however, that it is concerned in some fashion with growth, serving possibly—as suggested by Javillier, Delezenne, and Piccinini—as a sort of biologic catalyzer to promote the efficiency of growth processes.

In order to evaluate intelligently the effects of zinc introduced abnormally into the mammalian body, a clear understanding is necessary not only of the widespread normal occurrence of zinc in animal tissues, organs, and excreta, but also of the much more subtle problem of its significance to the living organism. Further work is greatly needed in order to shed light on the physiologic rôle of a metal so omnipresent in living matter.

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INCIDENCE OF DISEASE AMONG HOSPITAL PATIENTS, WITH REFERENCE TO OCCUPATION*

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The Deficiencies of Hospital Statistics

CRITICIZING hospital reports for the dearth of significant facts aside from "the dry bones of housekeeping and the hotel register," Harvey Cushing (1) points out the uselessness of publishing page after page of occupational affiliations of hospital patients without correlating these with the diseases for which they were treated at the hospital. "Though amusing," he says, "it is of no great interest to know that 1 umbrella mender or 1 gill box tender in a worsted mill, 1 strap finisher in an artificial limb factory . . . entered the hospital. What might be of value . . . . is to know what ailments these various people presented—the 20 barbers, the 84 carpenters, the 99 clerks, and 970 without occupation—to see whether their tasks, or absence of tasks, had any possible bearing on their disorder, but even this would hardly be worth while when numbers rarely run over two figures." It is a rare hospital where the number of patients of one occupation run into hundreds in one year and it is still rarer to find a hospital where the *minutiae* of occupation are inquired into. As a rule, the occupation is entered in a perfunctory manner and under general terms, and yet two persons described by the same occupational designation may be exposed to totally different hazards. Extensive studies of occupational disease cannot be made on the basis of the average run of hospital records, but gross statistics indicating tendencies in certain directions and suggesting detailed inquiry can and should be gathered. The value of such general data increases, of course, in proportion to the mass of experience. The cumulative experience of several years is more valuable than that of a single year, and the joint figures of many hospitals are more informing and significant than those of a single hospital. This applies to all phases of hospital statistics, and not only to the incidence of disease with reference to occupation.

An Experiment in "Pooling" Hospital Statistics

Following the recommendation of the Public Health Committee of the

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New York Academy of Medicine, the Hospital Information Bureau of the United Hospital Fund addressed a group of hospitals in New York City and offered its aid in a demonstration of the value and practicability of a central statistical service. Six hospitals agreed to co-operate by furnishing the Bureau with what practically amounted to copies of the discharge records of the patients, giving in each instance the age, sex, marital condition, occupation, citizenship, length of stay in New York City, principal ailment, complications, surgical operation, length of stay in the hospital, and condition on discharge. These records were edited in the office of the Bureau, and the information was transferred to punch cards for tabulation. The data lend themselves to numerous correlations (2).

What is presented in this paper is a brief summary of the incidence of the principal groups of diseases among certain broadly classified occupations. It is based on the experience of the following six general hospitals in New York City for the year 1923: Lincoln Hospital (with a large ambulance service), Lenox Hill Hospital (only ward patients recorded), Beth Israel Hospital, Carson Peck Memorial Hospital, Jewish Hospital of Brooklyn, and Brownsville and East New York Hospital. There were 20,835 patients reported from these hospitals in 1923, of whom 6,544 were children under 15 years of age. This number constitutes approximately 6 per cent. of the patients treated annually in all of the hospitals of New York City, many of which are devoted to the care of special conditions. The existence of numerous and large special hospitals, such as those devoted to the diseases of the eye, ear, nose, and throat, to gynecology and obstetrics, neurology, skin diseases and cancer, tuberculosis, etc., vitiates to a certain extent the statistical value of the relative incidence of disease among patients of the several general hospitals. The fact that three of the six hospitals from which records were obtained were predominantly Jewish in their clientele is another disturbing factor in so far as the general range of occupations and, to a lesser extent, the incidence of ailments are concerned.

Method of Tabulation

In preparing the tables on the incidence of diseases in relation to occupation, the children under 15 years of age were omitted, thus leaving 14,291 patients as the basis for tabulation. Before the summary analysis is presented, a few words must be said in explanation of the occupational and disease groupings. On their receipt in the office of the Hospital Information Bureau, all certificates were edited and the items on them given code numbers. The medical code was prepared on the basis of the International List of Causes of Death and of the Bellevue Hospital Medical Nomenclature. The code for occupations was based on the Classified Index of Occupations, published by the Bureau of the Census, United States Department of Commerce, for 1920. When the assorting of data was completed, it was found that there were over 600 separate pathologic entries distributed among patients of 350 occupational affiliations. It became at once obvious that, considering the comparatively small number of

cases, it would be impractical to attempt any detailed tabulation until the pathologic conditions and the occupations had been assembled in related groups. The grouping of the diseases was comparatively simple, the recommendations of the Committee on Industrial Morbidity Statistics (3) being followed with certain minor modifications. The grouping of occupations was a more difficult task. In conference with Dr. W. Gilman Thompson and Dr. Wade Wright, the matter was discussed at great length and the classification of diseases as worked out by Dr. Wright at the Massachusetts General Hospital was followed with certain abbreviations, as in many instances there were not enough cases of certain occupations to warrant making separate entries. No occupation was tabulated separately if it included less than ten persons. Several occupational designations were added to Dr. Wright's list. The occupations were finally reduced to fifty-nine; fifteen were classified among outdoor occupations, and forty-four among indoor occupations. The housewives were classified as a separate group, as were those who were not engaged in any occupation or for whom no occupation was reported by the hospitals.

Of the total number of 20,835 patients treated during 1923 in the six New York hospitals already mentioned, 14,291, or 68.5 per cent., were over 15 years of age and, therefore, of legal working age. Of these, 1,047, or 7.3 per cent., were classified as engaged in outdoor work and in this group were included those engaged in farming and gardening, those following seafaring pursuits, those employed in construction work, policemen, railroad and street transportation employees, and delivery men. The indoor occupations included factory workers, indoor construction workers, salespeople, office clerks, domestic servants, those in the professions and in executive positions. This group comprised 5,275 persons, or 36.9 per cent., of the patients over 15 years of age. Housewives constituted the largest single group—6,627, or 46.4 per cent. of the total workers of legal working age. The occupationally nondescript made up the rest of the patients—1,342, or 9.4 per cent.

Sex and Age Distribution of Patients

The sex distribution of the hospital group under consideration was preponderantly female—5,532 men and 8,759 women. There were no women in the outdoor group of occupations. In the indoor group of workers, approximately 72 per cent. were men and 28 per cent. women. In the unclassified group, the sex distribution was about equal, having a slight preponderance of males. About 35 per cent. of the members in the unemployed group were between the ages of 15 and 19, the sex distribution being the same in this age classification. This group includes likewise the highest proportion of patients over 60 years of age. In making deductions, if any, from the facts which the limited hospital experience subsequently analyzed presents, it is essential to keep constantly in mind the age distribution of the occupational groups in question. It is for this reason that Table 1, indicating the age classification by occupa-

TABLE 1.—MEDIAN AGE OF WORKERS IN VARIOUS OCCUPATIONS AS REPORTED IN 1923 FOR PATIENTS IN SIX NEW YORK HOSPITALS: LENOX HILL, LINCOLN, CARSON PECK, JEWISH, BETH ISRAEL, AND BROWNSVILLE

OCCUPATION	SEX	MEDIAN AGE
All patients	.....	32
	male	37
	female	30
Outdoor	male	36
Indoor	male	37
	female	25
Housewives	female	31
Unoccupied	male	39
	female	28
Outdoor:		
Farmers	male	47
Sailors, etc	male	43
Laborers	male	38
Masons	male	45
City fire department	male	32
Watchmen	male	57
Policemen	male	36
Steam railroad workers	male	
on trains	male	28
not on trains	male	33
Street railroad workers		
on cars	male	33
not on cars	male	39
Delivery men	male	36
Garage men and chauffeurs	male	28
Junkmen, etc	male	50
Canvassers, collectors, etc.	male	39
Indoor:		
Bakers	male	43
Miscellaneous food workers	male	50
	female	49
Candy cookers	male	29
	female	22
Butchers, etc	male	40
Cooks	male	39
	female	50
Garment factory workers	male	40
	female	23
Textile factory workers	male	35
	female	18
Shoe, etc., workers	male	49
Cigar and tobacco workers	male	41
	female	25
Plasterers	male	45
Plumbers	male	32
Painters	male	42
Woodworking factory workers	male	44
Carpenters	male	47
Blacksmiths, furnacemen, etc	male	38
Machinists (metal), etc.	male	34
Other metal factory workers	male	35
Tin and sheet metal workers	male	38
Jewelers, goldsmiths, etc.	male	34
Other miscellaneous manufacturing workers	male	38
	female	22
Electricians	male	26
Stationary engineers	male	41
Typesetters	male	35
Printers	male	29
Laborers	male	38
Elevator operators	male	33
Laundry operators	male	35
	female	34
Charwomen, etc	female	45
Barbers	male	40
Domestic servants, etc.	male	39
	female	29
Hospital workers	male	42
	female	22
Dressmakers	female	28
Salespeople (in stores)	male	30
	female	25
Retail storekeepers	male	41
	female	31
Office clerks	male	24
	female	21
Stenographers	female	21
Telegraph operators	male	29
	female	19
Telephone operators	female	22
Artists, authors, etc.	male	43
	female	28
Musicians	male	46
	female	28
Showmen, acrobats, etc.	male	33
Professional	male	38
	female	34
Semiprofessional	male	44
	female	38
Executive officers	male	42
	female	28

tion, is presented in addition to Table 2 giving the classification of disease by occupations. Figure 1 gives a visualization of the age group distribution of the patients in the principal subdivisions.

From Figure 1 it will be seen that the male outdoor and indoor workers presented a more uniform age distribution than any other group, and that these two groups resemble each other very closely with respect to age dispersion. Those in the unclassified group—*i.e.*, those who were either unoccupied or for whom the occupation was unstated—show a very similar age distribution for both sexes. It differs from the occupational groups in that 50 per cent. are in the age groups under 30, and a very considerable proportion in the age groups over 60 years of age.

TABLE 2.—COMPARISON OF PERCENTAGE DISTRIBUTION OF THE PRINICPAL DISEASE GROUPS AMONG THE SEVERAL OCCUPATIONAL CLASSES, BEFORE AND AFTER THE ELIMINATION OF "ACCIDENTS" AND CONDITIONS ASSOCIATED WITH THE PUERPERAL STATE

DISEASES	ALL PATIENTS (15 YRS. OLD AND OVER)		OUTDOOR WORKERS		INDOOR WORKERS		HOUSE-WIVES		UNOCCUPIED PATIENTS	
	Incl.	Excl.	Incl.	Excl.	Incl.	Excl.	Incl.	Excl.	Incl.	Excl.
	%	%	%	%	%	%	%	%	%	%
Epidemic, endemic, and infectious	4.6	6.4	8.1	10.7	6.6	7.3	2.4	4.7	4.2	4.5
General, not included above	10.0	14.1	12.8	16.9	11.9	13.1	8.0	15.5	11.0	12.0
Nervous system	4.7	6.6	4.8	6.3	6.0	6.6	2.9	5.7	8.2	8.9
Circulatory system	7.0	9.8	7.8	10.4	9.2	10.2	4.3	8.4	11.0	12.0
Respiratory system	5.1	7.1	8.6	11.4	6.8	7.5	2.9	5.7	6.4	7.0
Digestive system	25.0	35.0	21.9	28.9	35.6	39.6	14.7	28.5	36.4	39.6
Genito-urinary system	10.8	15.1	4.4	5.8	8.4	9.3	13.9	26.9	10.1	11.0
Skin	1.5	2.1	3.2	4.2	2.3	2.5	0.6	1.1	1.6	1.7
Bones	1.5	2.1	2.7	3.5	1.9	2.1	0.9	1.7	1.9	2.1
Ill-defined, not stated, etc.	1.1	1.5	1.4	1.9	1.4	1.5	1.0	1.8	0.4	0.5
Puerperal state	22.2	....	....	....	2.5	....	45.4	....	2.8	....
Accidents	6.5	....	24.3	....	7.4	....	3.0	....	6.0	....
Totals	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

The median age of female indoor workers is about 25, while that for housewives lies in the age period between 30 and 34. For groups of occupied males in both outdoor and indoor work, the median age falls in the age period between 35 and 39. (See Table 1 and Fig. 1.)

Relative Incidence of Disease

General Comparisons

It has previously been mentioned that women constituted the major part of the patients over 15 years of age in the six hospitals under con-

sideration. Over 45 per cent. of the women were in the hospital for conditions associated with puerperium. It might have been desirable to eliminate these cases in order to ascertain a truer distribution of the incidence of the various diseases among the occupational groups, uninfluenced by nonoccupational hazard. It might likewise have been desirable to eliminate from among the disabilities due to accidents those which were caused by nonoccupational hazards. Since, however, conditions of childbirth and pregnancy were reported among the gainfully employed women, and since the hospital records failed to differentiate between accidents of occupational and nonoccupational character, the proposed eliminations were not carried out, although it is realized that the relative proportions of other diseases are thereby disturbed to an appreciable extent, as seen from Table 2. Whether one uses the inclusive or the exclusive figures, it is evident from the table that the diseases of the digestive tract and the so-called "general diseases" lead in frequency, followed in the descending order by the diseases of the genito-urinary, circulatory, respiratory, and nervous systems. This order of frequency distribution is somewhat changed in the several groups of patients. Among the outdoor workers the respiratory diseases occupy the third place, while they are the fifth in order of relative importance among the indoor workers; and then while in the indoor group, heart and circulatory diseases hold the third place, they are two rungs lower on the ladder measuring their relative position among outdoor workers. In the housewife group, the order is entirely different. After the troubles of digestion come gynecologic conditions,

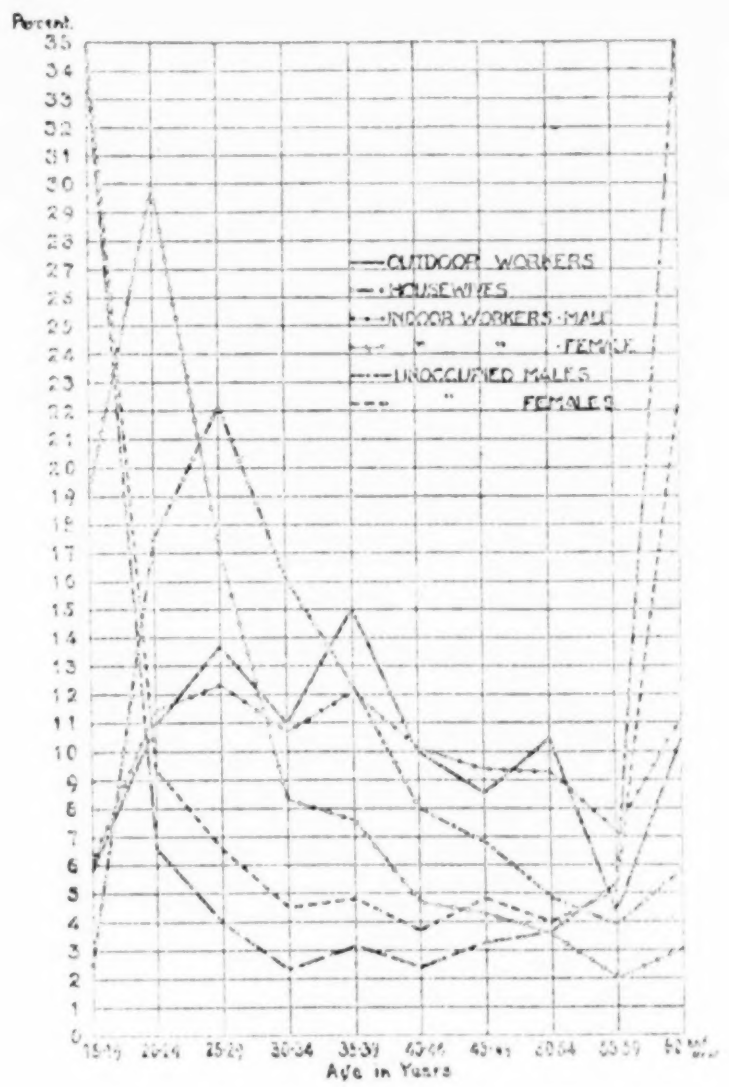

FIG. 1.—The age distribution of hospital patients by sex and character of occupational association.

followed by "general diseases," and those of the circulatory, nervous, and respiratory systems, in the order named. The unoccupied group has an order of its own, owing probably to the fact that it is composed in almost equal proportions of males and females and has of all groups the highest proportions of the young under 19 and of the old over 60. The relative importance of the various disease groups in the descending order is as follows: digestive, "general," circulatory, genito-urinary, neurologic, and respiratory.

Detailed Comparisons by Type of Occupation

In the description of the relative incidence of certain specified diseases, the rates in each instance are based on the totality of hospital experience and not on the exclusive tabulations in Table 2.

In the group of 1,047 outdoor workers, the outstanding single cause of hospital confinement was to be found in accidents, which amounted to almost one-fourth of all the cases. Of the accidents "fractures" constituted by far the greatest single item. As stated above, the hospital records from which the tabulations were made do not indicate whether these fractures were sustained during the course of occupation or outside of work; for this reason these figures do not accurately reflect the occupational hazard. Fractures do, however, occur in every eighth outdoor laborer treated in the hospital, in every fourth mason, in every second railway train operator, in every sixth delivery man, and in every tenth garage worker and chauffeur; to this extent these figures are perhaps significant. In the outdoor group as a whole, broken or crushed bones were found in every tenth worker; while among the indoor workers as a group the incidence was one in every thirty-three patients. Fractures were frequent among certain of the indoor workers to the extent of one in seven among the metal factory workers and elevator operators, and one in eight among plumbers.

The incidence of respiratory diseases was 8.6 per hundred among outdoor and 6.8 per hundred among indoor workers. In both groups the pneumonias constituted the largest single disease entity. The cases of respiratory diseases were scattered through the various specified occupational groups and were too few in each classification to warrant any deductions.

Among the diseases designated in the International List of the Causes of Death as "general," influenza, tuberculosis, cancer, venereal diseases, alcoholism, rheumatism, and chronic poisoning were most frequent among the patients treated.

There was more influenza (3 per hundred) among the outdoor than among the indoor workers (2 per hundred). Among the housewives and the unoccupied it occurred in the proportion of about 1 in every 100 patients. The highest incidence of influenza was among domestic servants (4 per hundred) and among hospital workers (5 per hundred).

The incidence of phthisis among the two principal groups of occupations and among the unoccupied patients ranged around 1 per hundred, but was only 2 per thousand among the housewives. The highest rates of pulmonary tuberculosis were found among domestic servants and office clerks, although in no instance was the incidence higher than 1.5 per hundred.

The venereal diseases (predominantly syphilis) were found as a primary condition at the rate of 8 in each 1,000 patients; among the outdoor workers the rate was 23 per thousand and among the indoor workers 12 per thousand.

The general rate of cancer in the hospital population was 3.4 in every 100 patients. Among the outdoor

workers the rate was 3.1; among the indoor workers it was 4.2. Among the housewives it was considerably lower—2.8 per hundred—and among the unclassified it was 3.7. The incidence of cancer was found quite high among food handlers (9.2 per hundred), carpenters (9.6), executives (7.6), professional men (over 5), and domestic servants (about 5). The age distribution of these occupational groups was dissimilar, the group with the highest percentage of patients over 40 years of age was that of the food handlers.

Rheumatism troubled only 1.1 per cent. of the outdoor workers as against 1.6 per cent. of the indoor workers. It seemed to have attacked garment workers to the extent of almost 3 patients in every 100 of that industry, more than any other occupational group of any size.

Alcoholism, acute and chronic, constituted 1.3 per cent. of the conditions treated, exactly as much as valvular disease of the heart. Considering that none of these hospitals was a municipal institution, this is a surprisingly high incidence. It was found in 8 per cent. of outdoor laborers and delivery men, in over 7 per cent. of indoor laborers, in almost 5 per cent. of hospital employees, and in over 2 per cent. of office clerks.

Thirty-eight in each 10,000 patients suffered from acute and chronic poisoning as a primary condition for which they were admitted to the hospital. The rate of occurrence among outdoor workers was 66 per ten thousand, among indoor workers, 61, and among housewives, 21; no cases were reported among the unclassified. Altogether too few cases were reported under this head to justify any analysis by individual occupations.

Just as in the case of tuberculosis the majority of the recognized cases receive treatment in special hospitals, sanatoriums, and clinics, so in cases of well-recognized nervous diseases, special accommodations are sometimes sought. The total number of 260 cases in a group of 14,291 may, therefore, be an underestimate of the incidence of neurologic diseases in the City population. It constitutes an average of 1.8 per hundred of the hospital sick. Neurologic diseases were found in 2 per cent. of both the outdoor and the indoor workers; in only 1.5 per cent. of the housewives; and in 2.5 per cent. of those who were either unoccupied or for whom the occupation was unstated. The incidence among the garment workers and domestic servants was higher than among any other large occupational group, reaching 3 per hundred.

The diseases of the organs of special sense are likewise often segregated in special institutions. For this reason the incidence found in general hospitals may likewise be somewhat lower than would be the case if the experience of all the hospitals of the community were combined in one statistical pool. The incidence of the diseases of the eyes was somewhat higher than that of neurologic conditions. These diseases were reported in 4 per cent. of the office clerks and patients without occupations. Ear diseases were found to constitute less than 1 per cent. of conditions for which the patients were treated in the hospitals.

Of the diseases of the circulatory system which are assuming a dominant

position in our mortality bills, those affecting the heart are the most important. In the group of 14,291 patients, 413, or about 3 per cent., had cardiac involvement; 220, or 1.5 per cent., arterial disease; and 256, or 1.8 per cent., impairment of the veins. Outdoor workers suffered from heart disease in the proportion of 3.5 per hundred, indoor workers 3.7 per hundred, those in the unoccupied group 5 per hundred, and the housewives less than 2 per hundred. Among the garment workers and painters, heart disease was found in 6 out of every 100 employees; among carpenters the rate was somewhat lower, and among indoor laborers over 7 per hundred. These rates, as many others, are computed on too small a number of cases to make them significant. They argue, however, for a wider utilization of hospital statistics as a basis for scientific medico-statistical research and social policy.

Diseases of the arteries are relatively more frequent among indoor than among outdoor workers and show the highest incidence in the fourth main group, *i.e.*, those without occupation. The bulk of the diseases of the veins were hemorrhoids and varicose ulcers; only a very small proportion were other diseases of the veins and half the number of these cases were among the women housekeepers.

Diseases of the digestive tract occupy a dominant position in the pathogeny of *homo sapiens*. The largest number of patients in this category were treated for appendicitis, 1,087 out of 14,291, or 7.5 per cent. Almost 12 per cent. of the indoor workers were its victims as against less than 5 per cent. in the outdoor group. The unclassified group had an incidence of over 11 per cent. The housewives succumbed to appendicitis in the smallest proportion (about 4 per cent.), while stenographers, salespeople in stores, storekeepers, and garment workers were the favorite victims, showing rates of 28, 18, 14, and 13 per hundred, respectively.

Hernias and intestinal obstruction were the second group in point of number of disorders of the digestive tract, constituting 4 per cent. of all the pathologic entries. Sixteen per cent. of the bakers in the six hospitals were treated for this condition; 15.4 per cent. of the butchers; 13 per cent. of the carpenters; 9 per cent. of the food handlers; 6.5 per cent. of the outdoor laborers; and 5.4 per cent. of the garment workers.

The highest relative proportion of gastric and duodenal ulcers was found among food handlers in whom this condition constituted 7 per cent. of ailments; while in the whole group of hospital patients this condition showed an average incidence of 1.4 per cent.

"The slaughter of the tonsil" was considerable. Over 5 per cent. were relieved of this encumbrance. It is quite significant that 30.7 per cent. of the patients who were employed in hospitals had their tonsils taken out; office clerks and stenographers were second with an average of 14 per cent.; and those of the professions 12 per cent.

Cholecystitis was found in 2.7 per cent. of the patients. The incidence of it showed no particular concentration among the several occupational groups. It was higher than the average among the housewives, 249 cases in a group of 6,626 women, or about 4 per hundred.

The diseases of the kidneys constituted about 1.3 per cent. of the cases. The rate was about 2 per cent. among office clerks and somewhat over that among food handlers; the cases, however, were too few to make this in any way indicative of an existing correlation.

Comparisons by Age Groups

An analysis was also made of the age and sex of the workers in each occupation. The method used was to divide the workers in each occupation into three age groups: a younger group, including all workers under 30 years of age; a middle group, including those from 30 to 49 years; and an older group, comprising all workers 50 years of age and over. On the basis of this age grouping the occupations were then classified into "younger," "middle," and "older."

Among the workers in occupations classified in the younger age groups, the commonest conditions, in the order of their frequency, were: appendicitis, diseases of the tonsils, hernia, and intestinal obstruction. In ten of the nineteen occupations in the younger group, appendicitis occupied first place in point of frequency. In the occupations of the middle age groups, appendicitis and hernia were first and second in order of importance, and fractures third. In the occupations of the older age groups, cancer and lobar pneumonia were most frequent.

Conclusion

The data which are briefly analyzed in this paper bring out certain interesting and suggestive facts concerning the incidence of disease. Although often inconclusive *per se* because they are based on too narrow a foundation, they are nevertheless valuable as pointing the need of a more intensive use of medical statistics of hospitals and of establishing a national agency for the collection, tabulation, and interpretation of the huge mass of hospital experience, which only too often is allowed to lie fallow and useless in the archives of the institutions.

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OBSERVATIONS ON MILD CYANIDE POISONING: REPORT OF A CASE*

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THE literature with respect to poisoning by hydrogen cyanide gas refers chiefly to cases of acute and fatal poisoning and their symptoms. Chronic and recurring mild poisoning has been observed in very few instances. It seems worth while, therefore, to describe the following case.

A short time ago there came to the Industrial Clinic at the Massachusetts General Hospital a patient who had been working in the photographic dark room used in a wet plate process and had suffered on three different occasions from symptoms resembling those of cyanide poisoning. One of the steps in this process involved the use of a dilute solution of potassium cyanide. The apparent danger in the process lay in the workman's standing over a sink containing about a liter of ferrous sulphate solution previously washed from the plate to be developed. An equal quantity of 30 per cent. potassium cyanide solution was next poured on the plate and washed into this same sink. If the sink did not drain quickly a chemical reaction took place, liberating cyanide gas. With slow drainage and inadequate ventilation, under extra pressure of work considerable cyanide gas could accumulate in the air of the room, particularly just above the sink.

* Received for publication Feb. 17, 1926.

Case Report

The patient was a young man aged 20, thin and somewhat pale, but apparently healthy. While at work developing plates, he had, over a period of two weeks, three attacks of numbness, weakness, vertigo, some nausea, rapid pulse, and flushing of the face after one hour's work. These attacks came at the end of the week each time and were followed the next day by headache and vague gastric distress with a rapid return to normal. One attack occurred after an unusual amount of work during which a 4-liter jar of the potassium cyanide solution used had to be emptied into the sink and a fresh solution made. The first solution had by mistake been made more concentrated than the required 30 per cent. The patient was one of three engaged in developing plates and had been working a year before these symptoms occurred. The other two men had no complaints.

The patient gave a history of measles and diphtheria in childhood, and acute infectious arthritis, lasting four

months, at the age of 12. His tonsils and adenoids had been removed eighteen months before he was seen at this Clinic. His habits were excellent, except that he was working hard and was going to night school several times a week. His family history was negative.

Physical examination was negative except for the heart signs and blood condition. There was distinct evidence of well-compensated mitral disease with a suggestion of aortic disease as well. Systolic blood pressure was 135, diastolic 40. The hemoglobin was 80 per cent. (Tallqvist), the red blood count 4,600,000, and the white count 8,200. The patient was first seen when all the effects of his last exposure had passed away, so that none of the transitory indications typical of cyanide poisoning appeared in his blood or his blood pressure at the time of the examination. Neither was there any odor of bitter almonds to his breath.

From the history, it seems evident that the attack described might have come from either (1) a heart condition, (2) increased susceptibility to cyanide poisoning due to the heart condition, or (3) from poisoning by cyanide gas alone.

Symptomatology

Typically, cyanide poisoning by inhalation is due to internal suffocation in the presence of abundant oxygen. Hydrogen cyanide is a protoplasmic poison retarding oxidation. The tissues no longer absorb oxygen and the venous blood is bright red. The symptoms of moderate nonfatal poisoning are a feeling of apprehension, faintness, muscle tremor and weakness, palpitation of the heart, and then a splitting headache and nausea. The respiration is rapid at first and then it becomes slow. Occasionally, the blood pressure is elevated at the time. Temporarily, the red blood count may be reduced and there may be destruction of hemoglobin; the white count is not reduced (1) (2) (3).

A somewhat similar symptomatic picture might be presented by a cardiac attack. That the heart condition alone was responsible for these attacks seems unlikely in this case since no such symptoms had appeared before and none appeared after the patient left this particular job. It seems likely that the heart condition made the patient more susceptible to the effect of the cyanide gas than the other men in the room who were not affected at any time. The slight reduction in red blood cells and the low hemoglobin were suspicious signs but did not seem marked enough to be significant.

Air Test

After the patient had these attacks, the ventilation of the dark room was improved by the addition of a blower and an exhaust fan with a hood. A test for the amount of cyanide gas in the room could, therefore, give very little idea of the conditions prior to these improvements. Nevertheless, it was thought that such a test would show the concentration of cyanide gas in the room with improved ventilation and would be a warning of any future danger. Accordingly, the air near the surface of the sink at about a 4-foot level, the general atmosphere of the room,

the air directly above the bottle of solution, and the air passing through the exhaust fan were all tested for cyanide content. The test used was that developed by Katz and Longfellow at the Bureau of Mines (4), with apparatus kindly provided by them.

The test showed that over the bottle of cyanide solution there was a concentration of 50 parts of cyanide gas per million parts of air. Tests taken about 6 inches above the level of the sink under the hood and in exhaust fan air showed 75 parts per million. A test of the general atmosphere showed between 25 and 50 parts per million. The experimental work done by the Bureau of Mines has demonstrated that a room which has a gas concentration of less than 100 parts per million is safe for human beings.

Considering the case in detail, it seems reasonable to assume that the disability of the patient, added to the possible large amount of gas which might have been liberated during a rush of work with inadequate ventilation and poor sink drainage might easily have caused mild recurring attacks of poisoning from the gas. Resumption of work under the improved conditions seemed entirely possible for the patient and this recommendation was made to his employers.

Conclusions

1. The literature reports very few cases of chronic or mild and non-fatal cyanide poisoning. It is doubtful whether this ever occurs to any extent.

2. Industrial poisoning as a cause of disease symptoms even when they seem typical of poisoning should not be assumed until organic disease has been eliminated.

3. In the case reported, temporary attacks of poisoning from this gas apparently did occur.

4. Poisoning from this substance under similar conditions can be easily prevented by proper ventilation and by rapid drainage of waste liquids which may produce gas formation.

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THE INDUSTRIAL SURGEON'S TREATMENT OF FRACTURES*

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TO DRAW a distinction between the methods employed by the industrial surgeon in the treatment of fractures and those employed by the general surgeon among private patients usually of the class engaged in less severe forms of labor, seems particularly appropriate at this time. Among all surgeons today the aim is unanimous and definite—to obtain perfect reposition of bones following fracture. Experience has shown that contact of fragments with no shortening will serve the needs of surgery satisfactorily when we fall short of perfect reposition. There is a wide divergence of opinion as to the methods of attaining these ends. In nonindustrial areas one frequently encounters surgeons who oppose open reduction of fracture in a good surgical risk when other methods have failed.

Recently in Scotland, Dowden[1] has published a book stressing motion in treatment of fractures of the upper extremity; reduction is not insisted on and fixation interfering with motion is discouraged. The book deals extensively with the good function attained by such methods. This is a tortuous way of getting return of function. Proper replacement permits of motion and assures quick return of function. Just as the X-ray when first used showed horrible displacement of bone fragments immediately following efforts at reduction, so today after the passage of years X-rays of the same cases have shown more or less beautiful results due to the stimulation of the efforts of nature by use over a period of years. These results are exceptional, and I would stress the passage of years, because a passage of years is necessary before such results can become manifest; however, these results are referred to constantly by so-called conservative surgeons who are satisfied when they fail in efforts at reposition or contact of fragments.

The premises for these arguments used by the so-called conservative surgeon serve the industrial surgeon more efficiently. They have shown him the wonderful resistant and reparative quality of bone. They have given his investigative mind a better idea of pathology of bone and enabled him to utilize this knowledge in obtaining the quick recovery of his patients.

* Received for publication March 3, 1926.

[1] Dowden, J. W.: The Principle of Early Active Movement in Treating Fractures of the Upper Extremity. Edinburgh, Oliver & Boyd.

For a decade I have been actively interested in disabled coal miners, and during this time my observations have covered over 20,000 accidents. Excepting eye injuries, empyema following injury, and a few decidedly rare injuries, all of our serious disabilities have resulted from fractures.

It is easily possible to cite isolated instances of badly crippled and deformed men who have quickly taken up their former labors. I recall a man with a fractured hip who went to the mine on crutches and crawled to his position underground. That this man is an exception goes without saying. That he would be able to obtain work easily is extremely doubtful and that his picture was a pathetic one is obvious.

The laborer must have, above all things, a substantial, bony framework. Without it the coal miner no longer mines coal. Among friends and acquaintances in the business world I can recall men with ununited fractures, malposition of fragments, artificial limbs, etc., who go through life apparently without handicap. They are the arbiters of their own fates. Certainly these conditions reflect no credit on the attending surgeon; but when the patient refuses proper efforts at reduction, the responsibility becomes his and he must be content with the result. Too frequently his refusal depends on ignorance of the results to be attained.

Fractures that are not placed in proper position within ten days become extremely difficult of reduction by any method. Previously I have laid stress on the necessity of reposition of fragments within ten days on account of beginning bone formation and tissue contraction and rigidity after the ten-day period. Failure of all closed methods for a period of ten days indicates open reduction, in the absence of the usual contraindications to operation. When satisfied that such efforts are failures, generally speaking operation should be undertaken any time between the fourth and the tenth day. This is dictum.

Barring the occasional transverse fracture, with no displacement, which shows fibrous union and which is easily and successfully treated by removing the fibrous tissue lying between the bone fragments or by doing in addition a reverse sliding bone graft, all serious disabilities show malposition. Some of them show nonunion as well. The most serious of these fractures involve the arms and legs. Unless there has been proper reposition of fragments, it is inevitable that the weight bearing forces coming on the foot are spent on different lines and result in pain in the foot on walking; in many cases of this kind the men say frankly that while walking on level sidewalks they are comparatively comfortable but when they are compelled to do the walking over rough ground to reach their work, they suffer such extreme distress as to make their return to work impossible. These complaints are unquestionably real. It is quite true that with the passage of years the discomfort incident to the use of such a leg may become negligible owing to the wonderful reparative process of nature; but with the passage of years the laboring man loses the moral urge to work and too frequently becomes a confirmed invalid. In addition he becomes a great economic loss.

J. I. H.
June, 1926

In industrial work where compensation laws are in operation, corrective surgery becomes imperative. First, human justice requires it; second, the injured man must regain his poise and his feeling of self-reliance by returning to work; third, pain and discomfort must be eliminated; fourth, the insurance company should properly discharge its obligation to employer and to society in general by returning injured men fit for their former work as quickly as possible. More pointed reason comes from the difficulty of impressing a referee with the fact that a man who has an obviously deformed arm or leg is able to return to his former work. Both referee and physician are willing to urge work upon the man who shows normal bone alignment. What has been said of the leg and foot applies with

FIG. 1.—End-result after second bone graft of ulna. First graft was fractured by a fall.

equal force to the arm and forearm, when we consider the many unusual movements required in perfect use of the hand.

In the absence of the usual contra-indications, I routinely plate displaced fractures of the clavicle. One plate is sufficient. It serves its purpose for a period of three to four weeks and is better removed under local anesthesia at the end of this time, for sooner or later its superficial position will cause discomfort and make removal necessary.

FIG. 2.—End-result after second bone graft of radius. First graft was fractured by muscular effort at work.

PROPER REDUCTION OF FRACTURES

Ice tong traction in contradistinction to the use of the Steinmann pin, the heel traction band, the Thomas' leg splint, the Thomas' arm splint, and the Balkan frame used in proper combination with traction and counter-traction have markedly reduced the number of instances in which operation must be resorted to for proper reduction of fractures. The proper reduction of all fractures is impossible. The proper reduction of all fractures of long bones is possible. My greatest difficulty has been in securing proper reduction of the overriding ends of the clavicle, radius, and ulna.

After failure to reduce fractures of one or both bones of the forearm by all means at my disposal, including direct vision under the fluoroscope, with my patient anesthetized, it is my custom to resort to open operation; where this has been necessary, open reduction with fragments grasped in large Lane bone holding forceps has sometimes been most difficult on account of muscular action and interposed muscular tissue. I have twice

seen death follow extensive open operation for reduction of fractures of the femur. Once in my own hands death followed shock. Laying aside this very rare occurrence, bone surgery is not shocking. In the presence of proper technic these patients routinely do well. Ordinarily they run a higher postoperative temperature than the abdominal case and frequently maintain a temperature for five days. Aside from this, convalescence is infinitely more satisfactory and less annoying than the convalescence of abdominal patients.

I am confident that with the institution of early proper reposition of fragments little corrective, reconstructive surgery will be necessary. Figures 1 and 2 show the end-results in two cases with fracture of the bones of the forearm. Figure 1 presents the end-result in a syphilitic patient who was sent to me showing good union of the radius and nonunion of the ulna. After first obtaining a negative Wassermann by treatment, a sliding bone graft of the ulna was done. This young man was extremely active, and while still carrying his arm in a cast and sling went hunting and fell, causing a refracture. The graft had not yet firmly united and had shown no regeneration. It was quickly absorbed. A second operation was done in which a graft was taken from the tibia. The X-rays were taken sixteen months after operation.

In Figure 2 is shown the end-result in a fracture involving the radius at the junction of the upper and middle thirds. This man was an ignorant alien incapable of proper understanding. He was a consistent drinker of "moonshine." Proper reposition by "closed methods" was impossible and I did a wiring operation. No union of the radius occurred. Later, a sliding bone graft of the radius was done. This man at my suggestion returned to work at a time which, I now know, was too soon after his operation. He refractured the arm at the site of the graft. A second bone graft, being the third operation, was again done in the form of a sliding bone graft. The pictures show the result after eighteen months. A small piece of wire lying in the soft tissue but causing no harm is also seen.

These two cases speak volumes for the tolerance and the regenerative power of bone tissue; the patients unquestionably have and show good serviceable arms.

If the industrial surgeon continues his efforts to obtain return to normal position and function, it is inevitable that sooner or later there will be but one thought on the proper treatment of fractures; and the general surgeon with this newer knowledge at hand will, together with his patient who sees the economic point of view, unanimously accept the industrial surgeon's dictum.

Reposition, fixation, and motion short of disturbing fixation epitomize present day fracture treatment.

DIE SCHÄDIGUNGEN DER HAUT DURCH BERUF UND GEWERBLICHE ARBEIT. Edited by *Karl Ullmann, Moriz Oppenheim*, and *J. H. Rille*. Paper. Volume II, Parts 1 to 4, pp. 192 and colored plates; Volume III, Parts 1 to 2, pp. 96. Leipzig: Leopold Voss, 1925.

The second and third volumes[1] of an exhaustive work on "The Occupational and Industrial Diseases of the Skin," by Ullmann and Oppenheim of Vienna and Rille of Leipzig, have just reached this country. These two volumes are abundantly illustrated and the plates are exceedingly good and clear. The same thing may be said of the printing, which leaves nothing to be desired esthetically and in point of legibility.

The first section of Volume II which is by Oppenheim has already appeared in English translation in THIS JOURNAL (1925, vol. 7, p. 407) and therefore needs no mention. It is followed by a chapter by R. Volk of Vienna dealing with the troublesome feature of oversusceptibility to the exciting causes of eczema or dermatitis. Volk speaks of disturbances of metabolism and systemic diseases (chlorosis, diabetes, liver and kidney disease) as predisposing causes and mentions the interesting phenomenon of the appearance of hematoporphyrin in the urine simultaneously with the outbreak of a rash on uncovered surfaces of the skin in men exposed to excessive light, such as glass blowers, blacksmiths, and iron molders. But far more numerous are those cases of individual idiosyncrasy with no recognizable physiologic basis. These cannot all be explained as anaphylactic in character; rather it is a matter of sensitization which may be specific for one substance or nonspecific, following exposure to various substances. The first may belong in the recently enlarged field of anaphylactic reactions, but the second could not.

The chapters on acids and alkalies, on halogens, on arsenic and antimony, sulphur, chromates, etc., are interesting but contain nothing particularly new. Among the newer occupational poisons which have an effect on the skin is calcium cyanamide, discussed by Koelsch who refers briefly to the interesting systemic effect of this powder as well as describing in detail its caustic action on the skin. Absorption of calcium cyanamide, if followed by indulgence even to a slight extent in alcohol, causes a profound vasomotor depression as noted in Germany, Italy, France, and the United States.

Another of the newer forms of dermatitis, or deep circumscribed ulcers, is described by Sachs in makers of acetylene gas by decomposition of calcium carbide with water. The skin lesions are due to the caustic action of the quicklime formed in this reaction. In Ullmann's chapter, eczema from the handling of phosphorus sesquisulphide in match factories is

[1] For review of Volume I, see THIS JOUR., 1925, vol. 7, p. 43.

described, and also the various forms of skin irritation from exposure to sulphuretted hydrogen fumes. In discussing arsenical lesions, the rather surprising statement is made that clinical and industrial experience shows that both the internal and the external action of arsenic compounds of all kinds, inorganic and organic, give rise to typical arsenical skin lesions such as erythemas, pigmentation, keratoses, trophic changes, and even carcinomatous degeneration. Although hydrogen arsenide is not specifically mentioned, this statement would seem to include it also.

In the chapter on mercury, Perutz considers the question of absorption and excretion through the skin. He points to the fact that the skin lesions which not infrequently follow the therapeutic use of mercury are very rarely seen in industry, and if a rash does appear it is not severe. On the other hand, lesions of the mucous membranes—mouth, stomach, and intestines—are very severe in industrial poisoning and rare or mild in nonindustrial poisoning. He quotes the experiments of Süssmann as showing that lead and mercury in fat soluble compounds are capable of penetrating the skin, the fats of the skin either saponifying them or converting them into salts of fatty acids. Under abnormal conditions of the skin such reactions may not occur, the mercury may remain in the skin and produce a local irritation, but no systemic effect. In such a case, the dermatitis has occurred because the metal has not been absorbed, and for the same reason it is not accompanied by systemic poisoning. The lesions caused by mercury are usually erythematous, like those of measles or scarlet fever, followed by exfoliation.

Interesting but rare lesions are described in Winkler's chapter on silver and in Finger's and Ullmann's (in Volume III) on syphilis of industrial origin. It is pointed out that the latter is rare because syphilis can be conveyed usually only by prolonged contact with friction, but in exceptional cases a quite fleeting contact has resulted in infection. In industrial cases the lesions are found on the lips, tonsils, face, hands, and fingers, the latter showing paronychia followed by fungous granulations and swelling of cubital and axillary glands. Glass blowers, musicians using wind instruments, cooks, laundresses, and chambermaids form most of the victims; except for the glass industry, however, these occupations furnish only an occasional case. There have been actual epidemics of syphilitic lesions of the lips in glass factories in France and Italy.

The literature following each chapter is abundant, and the work is in every way one of great value. It is to be hoped that before long a translation into English will appear and that the form in which it is published will be as attractive as is this German publication.—*Alice Hamilton.*

NECESSITY FOR CHANGES IN THE VENTILATION LAWS OF THE UNITED STATES. *L. Greenburg. Am. Jour. Pub. Health, Jan., 1926, vol. 16, pp. 13–22.*

Although his title implies a broader subject the author shows that the United States ventilation laws under discussion apply only to small schoolrooms. Consequently his paper is devoted to this one aspect of ventila-

tion. In the reviewer's opinion it is regrettable that this was not made clear in the title of the paper.

The history and development of ventilation is reviewed showing that the modern laws applying to schoolrooms resulted from the old carbon dioxide standards long since agreed by both hygienists and engineers to be misleading. These laws require the supplying of 30 cubic feet of air per minute per pupil, an amount far in excess of the physiologic requirements.

The author quotes McLure (see THIS JOUR., 1925, vol. 7, p. 292) as showing that these laws result in a great waste of money and also quotes the New York State Commission on Ventilation as showing that mechanical ventilation causes increased respiratory troubles as compared with window ventilation.

The author argues that these reasons (with others of lesser importance) are sufficient to justify a repeal of the present laws, in the twenty-four states where such laws exist, and the substitution therefor of laws requiring the use of window ventilation with gravity or fan exhaust as advocated by the New York State Commission on Ventilation. In his discussion of this paper, Dr. Palmer suggests a repeal of the present laws and a chance for window ventilation to compete on an even basis with mechanical ventilation where ventilation laws are in force. He points out that such open competition is illegal because window ventilation cannot give the 30 cubic feet per minute required by the laws.

In the reviewer's opinion the repeal of the laws is desirable and the substitution therefor of laws requiring such conditions as a comfortable temperature of 66° to 70°F., a relative humidity of 60 to 30 per cent. with freedom from drafts, and air reasonably free from impurities such as dusts and gases.

Dr. Palmer's suggestion will be more conducive of co-operation between public health workers and ventilating engineers than the more sweeping condemnation of mechanical ventilation asked by Dr. Greenburg.

As no statistical data have been published by the ventilating engineers in criticism or refutation of McLure's cost data or Dr. Greenburg's "increased respiratory disease" accusation, neither of Greenburg's accusations, in the reviewer's opinion, is as yet justifiable. That the advocates of mechanical ventilation for small schoolrooms have been delinquent in supplying or publishing these data is obvious. That the data are either unavailable or nonexistent has not been shown.—*Philip Drinker.*